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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/822,873	04/02/2001	Peter Kaastrup	KAASTRUP=1A	7206

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EXAMINER	
KIM, YUNSOO	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 06/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/822,873	KAASTRUP, PETER	
	Examiner	Art Unit	
	Yunsoo Kim	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,21-24,26-51 and 53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,21-24,26-51 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed on 5/4/05 has been entered.
Claims 2-5, 25 and 54-56 have been canceled.
Claims 1, 22 and 26 have been amended.

2. Applicant's Remark filed on 5/4/05 has been entered.
Claims 1, 21-24, 26-51 and 53 are pending.

3. As the original restriction mailed on 7/13/04 specifically set forth the election between SEQ ID NO:1 and a specific mutant of SEQ ID NO:1, the finality of the restriction is deemed proper and claims 6-20 will remain withdrawn.

4. The certified copy of foreign priority document on an application filed in Denmark PA2000 00540 on 3/31/2000 has acknowledged.

5. Upon cancellations of claims 2-5 and 25 and amendment on claim 26, the rejection under the second paragraph of 35. U.S.C. 112, (sections 9 and 10 of office action mailed on 12/17/04) and the rejection under the 35 U.S.C. 102, (section 13 of office action mailed on 12/17/04) are withdrawn.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out this invention.

Claims 1, 21-24, 26-51 and 53 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunogenic composition comprising of a TGF-beta fragment consisting of SEQ ID NO:1, does not reasonably provide enablement for an immunologic composition comprising "fragment" of TGF-beta as recited in claims 1 and dependent claims thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use of the invention commensurate in scope with these claims.

Applicant's arguments filed on 5/4/05 have been fully considered but they are not persuasive. Applicant argues that the single amino acid substitution by alanine scanning mutagenesis is not undue amount of experimentation and written description training material accept the combination of a 95% identity limitation. Applicant also argues conserved P1 and L18 positions serve as basis for mutations.

SEQ ID NO:1 has 3 alanine positions at 1, 4 and 5, having substitutions of given alanine residues to glycine residues, the 95% identity will not be met.

It is the examiner's position that it is undue amount of experimentation to substitute amino acid residues at non-conserved positions, there are $9.1X10^{27}$ different combinations for approximately 20 other non-conserved positions, for example, with a single amino acid substitution.

However, Applicant does not limit the claimed invention to either an immunogenic composition comprising a peptide consisting of SEQ ID NO:1 or immunogenic composition comprising a peptide consisting of SEQ ID NO:1 with a single amino acid substitution.

Applicant's specification of instant application on p. 18, lines 14-22, p.18-19 overlapping paragraph, or p.20-21 overlapping paragraph allows rather any addition, substitution, deletion of any amino acids, any number of amino acids from one or more to 10 amino acid residues or to 200 amino acid residues. The full-length TGF-b is encompassed within the scope of invention which allows 10-200 amino acids (addition of 83 amino acids to SEQ ID NO:1 results 112 amino acids, full length of TGF-b).

Applicant further argues that U. S. Pat. No.5,061,786 teaches a specific amino acid substitutions. The'786 patent teaches polypeptides derived from TGF-beta fragment various in lengths from 10 amino acids to 16 amino acids and the substitutions at "specific sites" within the polypeptides are immunosuppressive (see cols 3-5, in particular). Not only the functional equivalents comprising any TGF-beta fragment would be expected to have greater differences in their activities are taught but also specific guidance are given.

7. Claims 1, 21-24, 26-51 and 53 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's arguments filed on 5/4/05 have been fully considered but they are not persuasive.

As mentioned above, Applicant does not limit the claimed invention to either an immunogenic composition comprising a peptide consisting of SEQ ID NO:1 or immunogenic composition comprising a peptide consisting of SEQ ID NO:1 with a single amino acid substitution. Applicant's specification of instant application on p. 18, lines 14-22, p.18-19 overlapping paragraph, or p.20-21 overlapping paragraph allows any addition, substitution, deletion of any amino acids, any number of amino acids from 10 amino acid residues to 200 amino acid residues, the full-length TGF-b is encompassed within the scope of invention which allows 10-200 amino acids (addition of 83 amino acids to SEQ ID NO:1 results 112 amino acids, full length of TGF-b). The amendment to claim 1 does not overcome the rejection.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 21-24, 26-51 and 53 stand rejected under 35 U.S.C. 102(b) as being anticipated U.S. Pat. No. 5,874,085 (IDS reference 20, of record) and in further evidence of Schiott et al. (Scand. J. Immunol. 48, 371-378, 1998, IDS reference 50, or record).

Applicant's arguments filed on 5/4/05 have been fully considered but they are not persuasive. Applicant traversed the rejection based on the amendment to claim 1 to a fragment of TGF-b and the prior art of record does not teach the TGF-b fragment or limit to SEQ ID NO:1.

It is noted that Applicant does not limit the claimed invention to either an immunogenic composition comprising a peptide consisting of SEQ ID NO:1 or immunogenic composition comprising a peptide consisting of SEQ ID NO:1 with a single amino acid substitution. Applicant's specification of instant application on p. 18, lines 14-22, p.18-19 overlapping paragraph, or p.20-21 overlapping paragraph allows any addition, substitution, deletion of any amino acids, any number of amino acids from 10 amino acid residues to 200 amino acid residues, the full-length TGF-b is encompassed within the scope of invention which allows 10-200 amino acids (addition of 83 amino acids to SEQ ID NO:1 results 112 amino acids encompassing full length of TGF-b).

The '085 patent teaches a vaccine adjuvant comprising an antigen and TGF-beta (see Summary of the Invention including cols 3-4, in particular). The vaccine adjuvant comprises a carrier and additional adjuvant (see Use of the Claimed Composition including col 11, in particular). The composition is capable of eliciting immunostimulating effects, as well as increase in class of immunoglobulins, (see Description of Preferred Embodiments; col 6, lines 14-44, in particular), and enhances antibody response (see Description of Preferred Embodiments; col 8, lines 6-25, in particular).

In further evidence of Schiott et al. (Scand. J. Immunol. 48, 371-378, 1998), it was known the amino acid sequence of TGF-beta is highly conserved among TGF families (p. 371, Introduction, in particular). Given that TGF-beta comprises SEQ ID NO:1 and Schiott et al. teach the amino acid sequence of TGF-beta is highly conserved, the prior art teaching of TGF-beta anticipates the claimed TGF-beta which comprises SEQ ID NO:1. Thus, it meets the limitations found in the instant claims.

The '085 patent also teaches various combinations of either conjugated fragment, or non-conjugated fragment, either conjugated immunogenic determinant or non-conjugated immunogenic determinant and either conjugated or non-conjugated carrier including combinations of a) conjugated fragment and non-conjugated immunogenic determinant, b) non-conjugated fragment and conjugated immunogenic determinant, c) fragment and immunogenic determinant are conjugated, d) fragment is conjugated to immunogenic determinant, e) non-conjugated fragment and immunogenic determinant comprising a carrier, f) non-conjugated fragment and immunogenic determinant comprising a non-conjugated carrier, g) non-conjugated fragment and immunogenic determinant comprising a conjugated carrier, h) conjugated fragment and non-conjugated immunogenic determinant comprising a carrier, i) conjugated fragment and non-conjugated immunogenic determinant comprising a non-conjugated carrier, j) conjugated fragment

and non-conjugated immunogenic determinant comprising a conjugated carrier, k) conjugated fragment to carrier, l) non-conjugated fragment and conjugated immunogenic determinant comprising a either conjugated or non-conjugated carrier, m) conjugated fragment to immunogenic determinant comprising either a conjugated or non-conjugated carrier, as recited in claims 28-51 (see Use of the Claimed invention; from col 10, lines 60 to col 11, lines 39, and col 2, Table II in particular).

The '085 patent further teaches the use of TGF-beta fragments which retain the TGF-beta activity as intact TGF-beta (see Use of the Claimed Invention, col 19, lines 60-67, in particular). As the TGF-beta fragments retain the TGF-beta activity as intact TGF-beta, TGF-beta fragments are capable of eliciting the immunostimulating effects. The claimed functional limitations recited in claims 21-27 such as cytotoxic T-cell response, and increase level of T-cells and cytotoxic T-cells would be inherent properties of the immunogenic composition comprising TGF-beta and a vaccine.

As Applicant does not limit the claimed invention to either an immunogenic composition comprising a peptide consisting of SEQ ID NO:1 or immunogenic composition comprising a peptide consisting of SEQ ID NO:1 with a single amino acid substitution, the prior art teaching of TGF-b fragments (col. 10, lines 60-65) is well within the scope of the claimed invention and thus anticipate the instant claimed invention (see entire document including Use of the Claimed Invention and Examples).

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1, 21-24, 26-51 and 53 stand rejected under 35 U.S.C. 103 as being unpatentable over U.S. Pat. No. 5,874,085 (of record) as is evidenced by Schiott et al. (Scand. J. Immunol. 48, 371-378, 1998, of record), in view of U.S. Pat. No. 6,057,430 (of record).

Applicant's arguments filed on 5/4/05 have been fully considered but they are not persuasive. Applicant traversed the rejection based on the amendment to claim 1 to a fragment of TGF-b and the prior art of record does not teach the TGF-b fragment rather full length.

As Applicant mentioned SEQ ID NOs: 4 and 10 are indeed full length TGF-b sequences. However, '430 patent does not limit teachings to the full length TGF-b. Contrary to Applicant's argument, '430 patent teaches TGF-b fragment consisting of N-terminal 44 amino acids (which is equivalent to the first 44 amino acids to SEQ ID NO:4 or 10), or C-terminal 68 amino acids (which is equivalent to the last 68 amino acids to SEQ ID NO:4 or 10) (see col. 4-5 overlapping paragraph).

It is noted that Applicant does not limit the claimed invention to either an immunogenic composition comprising a peptide consisting of SEQ ID NO:1 or immunogenic composition comprising a peptide consisting of SEQ ID NO:1 with a single amino acid substitution. Applicant's specification of instant application on p. 18, lines 14-22, p.18-19 overlapping paragraph, or p.20-21 overlapping paragraph allows any addition, substitution, deletion of any amino acids, any number of amino acids from 10 amino acid residues to 200 amino acid residues, the full-length TGF-b is encompassed within the scope of invention which allows 10-200 amino acids (addition of 83 amino acids to SEQ ID NO:1 results 112 amino acids encompassing full length of TGF-b).

The '085 patent and Schiott et al. references have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of SEQ ID NO:1 in the claims.

However, the '430 teaches biologically active TGF-beta fragments consisting of N-terminal 44 amino acids or C-terminal 68 amino acid sequences depicted in the sequence listing under SEQ ID NO:4 or SEQ ID NO:1 (col. 4-5 overlapping paragraph). These biologically active TGF-beta fragments comprise of SEQ ID NO: 1 of the claimed invention. The biologically active TGF-beta fragments comprising of SEQ ID NO:4 or 10 are very potent biological agents which can be used therapeutically for different purposes. The fragments consisting of N terminal 44 amino acids or C terminal 68 amino acids of SEQ ID NOs:4 or 10 play a central role in many biological pathways including cell differentiation and wound healing (see col 2, lines 4-19, col 4, lines 29-59, col 4, lines 16-31, col, 4-5 overlapping paragraph and sequence listing in particular).

It would have been obvious to one of the ordinary skill in the art at the time the invention was made to employ the biologically active TGF-beta fragments (i.e. N-terminal 44 amino acids or C terminal 68 amino acids of SEQ ID NOs: 4 or 10) taught by the '430 patent in the immunogenic composition taught by the '085 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the TGF-beta fragments (i.e. N-terminal 44 amino acids or C terminal 68 amino acids of SEQ ID NOs: 4 or 10) taught by '430 patent are biologically active and therapeutically useful. As TGF-beta fragments would have the same immunostimulating effect as intact TGF-beta taught by '085 patent, it is expected that the TGF-fragments (i.e. N-terminal 44 amino acids or C terminal 68 amino acids of SEQ ID NOs: 4 or 10) taught by the '430 patent would elicit the same immunostimulating effect in the immunogenic composition.

From the teachings of references, it would have been obvious to one of ordinary skill in art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of the ordinary in the art at the time of invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

As indicated above, it is the examiner's position that the combination of teachings remains obvious.

12. The following new grounds of rejections are necessitated by Applicant's amendment to claim filed on 5/4/05.

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out this invention.

Claims 1, 21-24, 26-51 and 53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection for the following reasons:

The specification as file does not provide a written description or set forth metes and bounds of the phrase "or differs therefrom solely by a single amino acid substitution". The specification does not provide direction for the above mentioned phrases "or differs therefrom solely by a single amino acid substitution" as they are currently recited. The instant claims now recite limitations whish were not clearly disclosed in the specification as filed, and now change the scope of instant disclosure as filed. Such limitations recited in the present claims, which did not appear in the specification as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C.112.

14. No claims are allowable.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yunsoo Kim whose telephone number is 571-272-3176. The examiner can normally be reached on Monday thru Friday 8:30 - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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June 8, 2005

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